PHARMACY AND THERAPEUTICS REVIEW

Generic Name: Tiotropium

Proprietary Name: Spiriva HandiHaler®; Spiriva Respimat® (Boehringer Ingelheim)

Requestor /Reason for Request: Expanded FDA labeling for maintenance treatments of patients with asthma ≥ 6 years of age. After analysis of published literature, insurance preferences and increased hospital usage, both tiotropium formulations are recommended to be added to formulary.

Indications:[1-3] Tiotropium is indicated for the maintenance of patients with asthma ≥ 6 years of age in patients with a history of exacerbation. It is also used for the treatment of COPD in the adult population. Tiotropium is not indicated as a rescue inhaler.

Clinical Pharmacology:[2-3]Tiotropium is a long acting, antimuscarinic agent (LAMA) that inhibits M_3 receptors in the airway smooth muscle resulting in bronchodilation. The bronchodilation is dose-dependent and effects last longer than 24 hours. Maximum benefits may take up to 4-8 weeks of consistent dosing.

Pharmacokinetics:[1-3] Pharmacokinetic analysis in COPD patients compared Respimat inhaler (5 mcg) versus inhalation powder (18 mcg) via HandiHaler administration and found similar exposure between products. The absolute bioavailability after administration is 19.5%, suggesting high lung bioavailability. Peak serum concentrations are achieved 7 minutes after inhalation. Tiotropium is highly protein bound (72%) and has a large volume of distribution 32 L/kg after intravenous administration. The terminal t ½ in COPD patients after 5 mcg administration is ~25 hours. After chronic administration, pharmacokinetic steady state is achieved after 7 days with no further accumulation. There is minor non-enzymatic cleavage to inactive metabolites and minimal CYP450 (CYP2D6 and CYP3A4) oxidation and subsequent glutathione conjugation. Most tiotropium is eliminated unchanged via the urine (74%).

Adverse Reactions:[2-3] The most commonly reported side effects in >5% of patients included: upper respiratory tract infection, dry mouth, headache, sinusitis, pharyngitis, bronchitis, non-specific chest pain, urinary tract infection, dyspepsia, and rhinitis.

Dosing:[1-3] For the treatment of asthma, the recommended dose is 2 actuations (1.25 mcg/actuation) once daily. For COPD, the recommended dose is 2 actuations (2.5 mcg/actuation) once daily or 18 mcg (1 capsule) inhaled via HandiHaler once daily. There are no specific dosing recommendations available for patients with renal or hepatic impairment.

Product Availability/Storage/Cost:[1-3] Tiotropium is available from the manufacturer as an aerosol solution for oral inhalation via Respimat inhaler or as a dry powder capsule for inhalation via HandiHaler. Tiotropium should be stored at 25ºC, temperature excursions between 15-30ºC are permitted. Avoid extreme temperatures, moisture and freezing. The capsules should not be stored in the HandiHaler device but remain in the blister pack and removed immediately before use. Cost of the drug: 1.25 mcg/actuation ($128.84), 2.5 mcg/actuation ($55.67), 18 mcg capsule ($17.18/each)

Spiriva HandiHaler® is the preferred formulation by both Missouri and Kansas Medicaid.

Conclusion: Tiotropium is a safe and effective long-acting muscarinic antagonist that is preferred by private and public insurance providers. There is safety data and dosing information for patients ≥ 6 years of age for the treatment of asthma.

Recommendation: Recommend Spiriva® HandiHaler and Respimat be added to formulary due to increased utilization in the community and data regarding the safe and effective use for pediatric patients ≥ 6 years of age.

Full Monograph:

Generic Name: Tiotropium

Proprietary Name: Spiriva HandiHaler®; Spiriva Respimat® (Boehringer Ingelheim)

Therapeutic Class: Anticholinergic Agent; Long Acting Muscarinic Antagonist (LAMA)

Similar Drugs: Aclidinium (Tudorza Pressair), Revefenacin (Yupelri), Umeclidinium (Incruse Ellipta)

Indications:[1-3] Per current guidelines, tiotropium is indicated for the maintenance of patients with asthma ≥ 6 years of age in step 4 or 5 with a history of exacerbations despite combination inhaled corticosteroid (ICS)/long-acting beta agonist (LABA) treatment. Tiotropium is indicated for the treatment of Chronic Obstructive Pulmonary Disease (COPD) in the adult population only. It is not indicated as a rescue inhaler or for use in deteriorating disease.

Clinical Pharmacology/MOA:[2-3] Tiotropium is a long acting, antimuscarinic agent (LAMA) that inhibits M_3 receptors in the airway smooth muscle resulting in bronchodilation. The bronchodilation is dose-dependent and effects last longer than 24 hours.

Pharmacokinetics:[2-3]
Pharmacokinetic analysis in COPD patients compared Respimat inhaler (5 mcg) versus inhalation powder (18 mcg) via HandiHaler administration and found similar exposure between products. The absolute bioavailability after administration is 19.5-33%, suggesting high lung bioavailability. Oral solutions of tiotropium have an absolute bioavailability of 2-3%. Peak serum concentrations are achieved 5-7 minutes after inhalation after 4 weeks of once daily administration. Tiotropium is highly protein bound (72%) and has a large volume of distribution 32 L/kg after intravenous administration. Local concentrations in the lung are unknown, however, based on the method of administration substantially higher concentrations are expected in the lung. There is minor (~25%) non-enzymatic cleavage to inactive metabolites and minimal CYP450 (CYP2D6 and CYP3A4) oxidation and subsequent glutathione conjugation. The terminal t ½ in COPD and asthma patients is ~25 hours and ~44 hours, respectively. After chronic administration, pharmacokinetic steady state is achieved after 7 days with no further accumulation. Most tiotropium is eliminated unchanged via the urine (74%). The peak and total exposure to tiotropium was not found to be different between pediatric and adult patients. There are no specific dosing recommendations available for patients with renal or hepatic impairment for tiotropium administered via inhalation. However, for patients with severe renal impairment the AUC_{0-4} and Cmax were 94% and 52% higher, respectively, after patients received intravenous tiotropium.

Comparative Efficacy:[3]
The *Spiriva Respimat* package insert summarizes data from the clinical development program for asthma patients including data from 16 studies.

The dose for asthma was selected based on data from three randomized, double-blind, placebo-controlled, 4 to 8-week cross over studies in 256 adults, 105 adolescents (12-17 years of age) and 10 pediatric (6-11 years of age) patients. Results demonstrated numerical improvements in FEV1 at all doses compared to placebo; however, across the trials the response was not dose-ordered favoring the 2.5 mcg dose. In addition, 24 hour FEV1 results demonstrated comparable treatment effects for 2.5 mcg twice-daily compared to 5 mcg once daily dosing. Trials 1-5 were confirmatory randomized controlled trials between 12-48 weeks in adult patients on treatment of at least an ICS. These trials evaluated different dosing regimens and/or modified the enrollment criteria. The primary results are summarized in the table below:

Table 7 Differences from Placebo in Peak $FEV_{1, 0-3}$ and Trough FEV_1, Adult Confirmatory Studies at Primary Endpoint Time Evaluation

Treatment (Duration) *ICS Background Treatment* [b,c]	Treatment in mcg/day	n	Peak $FEV_{1, 0-3hr}$, in L [a]			Trough FEV_1, in L [a]		
			Δ from baseline	Difference from placebo		Δ from baseline	Difference from placebo	
				Mean	95% CI		Mean	95% CI
Adult patients, age 18 years and older								
Trial 1	SPIRIVA	154	0.29	0.16	0.09,	0.13	0.11	0.04,
(12 weeks)	RESPIMAT 2.5 mcg	155	0.13		0.23	0.02		0.18
Low dose ICS	Placebo							
Trial 2	SPIRIVA	259	0.29	0.24	0.18,	0.15	0.19	0.13, 0.24
(24 weeks)	RESPIMAT 2.5 mcg	271	0.27	0.21	0.29	0.09	0.12	0.06,
Medium dose ICS	Salmeterol 100 mcg	265	0.05		0.16, 0.27	–0.03		0.18
	Placebo							
Trial 3	SPIRIVA	256	0.29	0.21	0.16,	0.16	0.18	0.12, 0.23
(24 weeks)	RESPIMAT 2.5 mcg	264	0.25	0.18	0.26	0.09	0.11	0.05,
Medium dose ICS	Salmeterol 100 mcg	253	0.08		0.12, 0.23	–0.01		0.16
	Placebo							

[a] Means adjusted for treatment, center/country, visit, visit*treatment, baseline, baseline*visit.
[b] Additional asthma medications allowed in stable doses prior to and throughout the trials.
[c] Low dose ICS = 200–400 mcg budesonide-equivalent. Medium dose ICS = 400–800 mcg budesonide-equivalent.

Furthermore, studies evaluated exacerbation characteristics and found less exacerbation rate and increased time to first asthma exacerbation with treatment. The results of the trials support the efficacy in adolescent patients 12-17 years of age with asthma (mean difference in peak FEV from placebo for SPIRIVA RESPIMAT 2.5 mcg were 0.13 L (95% CI 0.03, 0.23) and 0.11 L (0.002, 0.22) for the 48- week and 12-week trials, respectively). Efficacy in pediatric patients 6-11 years of age was based on partial extrapolation of efficacy in adults and two randomized, double-blind, placebo-controlled trials of 12 and 48 weeks duration in a total of 801 asthma patients 6 to 11 years of age (271 receiving SPIRIVA RESPIMAT 2.5 mcg once-daily, 265 receiving 5 mcg once-daily, and 265 receiving placebo). Compared to placebo, SPIRIVA RESPIMAT 2.5 mcg once daily had a significant effect on the primary endpoint in the 48 week, but not the 12 week trial, with mean differences in peak FEV , from placebo of 0.17 L (95% CI 0.11, 0.23) and 0.04 L (95% CI -0.03, 0.10) for the 48-week and 12-week trials, respectively. Given the demonstration of efficacy in the adult and adolescent population, the results support the efficacy of SPIRIVA RESPIMAT 2.5 mcg once daily in pediatric patients 6-11 years of age with asthma.

Contraindications/Warnings/Precautions:[1-3] Hypersensitivity to ipratropium, tiotropium or any component of the product. Not indicated for acute use or as a rescue medication.

Tiotropium has also been associated with paradoxical bronchospasm. May cause dizziness and blurred vision, therefore, patients should not perform tasks that require mental alertness. Secondary to potential anticholinergic effects, use with caution in patients with glaucoma (may worsen symptoms of narrow angle glaucoma) and prostatic hyperplasia/bladder neck obstruction secondary to potentially worsening of symptoms.

Adverse Reactions: The most commonly reported side effects were pharyngitis, headache, bronchitis and sinusitis.

Drug Interactions: Anticholinergics: May interact additively with concomitantly used anticholinergic medications. Avoid administration of tiotropium with other anticholinergic-containing drugs.

Dosing:[1-4] For the treatment of moderate asthma in patients ≥ 6 years of age, the recommended dose is 2.5 mcg (2 inhalations of the 1.25 mcg/actuation formulation) once daily. Pharmacokinetic and bronchodilator efficacy studies suggest similar exposure and efficacy of 5 mcg of Spiriva Respimat® compared to 18 mcg (1 capsule) of Spiriva HandiHaler®.

There are no specific dosing recommendations available for patients with renal or hepatic impairment.

Products/Cost: Tiotropium is available from the manufacturer via Respimat inhaler as well as a dry powder for inhalation via HandiHaler. Drug should be stored at room temperature. Spirivia HandiHaler® is listed as a preferred agent by both Missouri and Kansas Medicaid. Per patient, therapy is approximately $8.10-9.39/day ($3,428 annually) depending on the formulation utilized.

All prices are reflective of Children's Mercy Kansas City purchasing group only.

- Spiriva Respimat 1.25 mcg/actuation (4 gm; 60 actuations): $281.81, $9.39 per day
- Spiriva Respimat 2.5 mcg/actuation (4 gm; 60 actuations): $362.32, $6.04 per day
- Spiriva Respimat 2.5 mcg/actuation (4 gm; 28 actuations): $36.56, $1.31 per day
- Spiriva HandiHaler 18 mcg capsule (5 capsules): $40.50, $8.10 per day
- Spiriva HandiHaler 18 mcg capsule (30 capsules): $398.56, $13.29 per day

Conclusion: Tiotropium has been evaluated in pediatric patients' ages ≥ 6 years. The safety and efficacy of these studies were similar to that seen in adult populations. Furthermore, the guidelines include the recommendation of tiotropium for moderate-severe asthma in patients ≥ 6 years of age.

Recommendation:[1-3] Recommend tiotropium be added to formulary due to increased utilization in the community and safety and efficacy in pediatric patients' ages ≥ 6 years of age as well as guideline recommendations for the treatment of asthma in patients ≥ 6 years old.

Reviewed by: Claire Elson, PharmD, BCPPS, Stephanie Duehlmeyer, PharmD

References:

1. Global Initiative for Asthma (GINA): Global Strategy for Asthma Management and Prevention. 2019. Available from: http://www.ginasthma.org/
2. Spiriva HandiHaler [package insert]. Ridgefield, CT. Boehringer Ingelheim Pharmaceuticals, Inc.; 2018.
3. Spiriva Respimat [package insert]. Ridgefield, CT. Boehringer Ingelheim Pharmaceuticals, Inc.; 2019.
Calverley PMA, Konen-Bergmann M, Richard F, et al. Tiotropium Respimat® Versus HandiHaler®: Comparison of Bronchodilator Efficacy of Various Doses in Clinical Trials. Adv Ther. 2016; 33: 786-93.